Translational Advances in Pain and Anesthesia for Cancer Patients

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Effective cancer pain management requires multidisciplinary approaches for multimodal analgesia. Although opioids have been the cornerstone, developments such as regional anesthesia and interventional pain techniques, complementary and alternative medicine, and new pharmaceuticals also have shown promise to relieve cancer pain. This overview of relevant clinical efforts and the modern day state of the science will afford a better understanding of pain mechanisms and multimodal approaches beneficial in optimizing analgesia for cancer patients.
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INTRODUCTION

Often inadequately treated by "standard" analgesic regimens, can cer pain remains a complex and significant problem facing clinicians today. The challenge to rapidly and effectively treat this pain has lead to a multidisciplinary pain management approach and a paradigm shift toward multimodal analgesia. Although opioids have traditionally been the cornerstone for management of chronic pain, many other non opioid agents have shown effectiveness. Techniques such as advanced regional analgesia, interventional pain procedures, and complementary and alternative medicine also have shown success and promise to aid in the battle against cancer pain. This brief overview of the relevant clinical efforts as well as the modern day state of the science will afford a better understanding of pain mechanisms and the multimodal approaches beneficial in optimizing control of cancer related pain.

While pain management is often cited as a major healthcare expen diture, optimizing pain control is about much more than just dollars and cents. It is about compassion, duty, and common sense. The amelio ration of unnecessary pain and suffering is a cornerstone of medicine. Inadequate pain management is something all clinicians must act upon. The burden of pain is enough to overwhelm an individual patient and their family when effective analgesia is not afforded. Along with the coincident and inherent mental anguish of being in pain at any given moment, sub optimal pain control is associated with increased incidence of long term sequelae such as posttraumatic stress disorder (PTSD) [1 3], depression, anxiety, non restorative sleep patterns, and of course, chronic pain syndromes. Even the ability to perform activities of daily living can be compromised when pain is not managed appropri ately. This can be a potential problem for thousands of cancer patients each and every year.

CLINICAL SYNOPSIS

Opiate receptor activation inhibits the presynaptic release and post synaptic response of excitatory neurotransmitters from nociceptive neurons [4]. Opioid receptor agents include both pure agonists (e.g., morphine, hydromorphone, oxycodone, fentanyl, and methadone) as well as agonist antagonists (e.g., buprenorphine, butorphanol, penta zocine, dezocine, and nalbuphine) [5]. Although chronic pain is most commonly treated with opioid agonists, buprenorphine has been shown to be the most useful of the agonist antagonists. In the sublingual form, it is potent, long acting and has been demonstrated to be an effective analgesic for the treatment of cancer pain [4].

Opioids can be delivered by different routes for better coverage of variable pain severity. While oral, transdermal, and parental tend to be the more common routes of administration, epidural and intrathecal opioids can interrupt the transmission of pain impulses at the level of the dorsal horn of the spinal cord with lower total doses of narcotics; resulting in less systemic absorption and fewer side effects [6]. The systemic side effects, including tolerance and dependence, limit the use of opioids for adequate pain control. This limiting factor emphasizes the importance of adjuvant therapy and the use of non opioid management for pain.

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Alternative pharmacologic interventions in pain management include prostaglandin synthesis inhibitors, N methyl D aspartate (NMDA) antagonists, alpha 2 agonists, antidepressants, anticonvulsants, and local anesthetics. These analgesics have proven to be effective individually in acute pain management and even more effective in combination as multimodal analgesia for the treatment of chronic pain [7]. The cyclooxygenase (COX) inhibitors, including salicylates, acetaminophen, and NSAIDs have varying analgesic, antipyretic, and anti inflammatory properties. The analgesia is due to blockade of prostaglandin synthesis, which sensitizes and amplifies nociceptive input, but is limited by side effects and toxicity at higher doses [8]. The newer COX 2 specific inhibitors may be of greater therapeutic potential due to their anti tumor and anti angiogenic properties [7,8]. The NMDA antagonist, ketamine, causes a dissociative anesthesia by functionally disconnecting the thalamus from the limbic cortex, thus reducing transmission and processing of the pain signal [5]. Its analgesic properties have proven useful in the management of both acute and chronic pain [7]. Although not available in the US for clinical use yet, the S stereoisomer, in particular, may be the next most promising analgesic medication.

Other pharmacologic interventions include clonidine and dexmedetomidine. Both alpha 2 adrenergic agonists block nociceptive transmission via activation of descending inhibitory pathways in the dorsal horn. Epidural and intrathecal clonidine has been shown to be particularly effective in neuropathic pain and opioid tolerance, but can be associated with hypotension and bradycardia [5,6]. Dexmedetomidine is seven times more selective for the alpha 2 receptor than clonidine, with dose dependent sedation, anxiolysis and analgesia [5]. Although clonidine is available in an oral form and can be used in conjunction with an oral regimen for chronic pain management, dexmedetomidine is only available parenterally, thus usually limiting it for short term in patient use. Antidepressants demonstrate an analgesic effect at doses lower than needed for their antidepressant action. This effect is due to the blockade of presynaptic reuptake of serotonin, norepinephrine, or both [5]. Older tricyclic agents appear to be more effective analgesics, can potentiate the action of opioids and frequently normalize sleep patterns. Anticonvulsants, notably gabapentin and pregabalin, have also been found to be extremely useful in patients with neuropathic pain related to cancer [9]. These agents block voltage gated sodium channels and can suppress the spontaneous neural discharges implicated in the pain pathway.

The anesthetics and analgesics chosen by clinicians for cancer patients can have a significant impact on oncologic outcomes, from traditional measures such as local control and survival, to more subjective but equally important concepts such as quality of life and pain control. In addition, patients in this population undergo unique procedures that have particular requirements with regard to anesthetic technique. Two broad categories of anesthetic use exist within this population: peri operative/peri procedural (during oncologic surgery or radiation procedures) and chronic pain management.

PERIOPERATIVE CARE AND PROCEDURAL PAIN

For many cancer patients, therapeutic interventions such as surgery may necessarily, but sometimes unknowingly, expose them to greater risk of clinical metastases or recurrence, based upon the selection of anesthetic. Proposed mechanisms involve impairments in host defenses against residual disease (malignancy) in the acute perioperative period as well as in long term rehabilitation [6,9]. Studies have shown that these three factors, which include: the physiological stress response to surgery, the impaired immune functions due to general anesthesia, and the inhibition of cellular and humoral immune functions with the use of opioids, can be minimized with the use of regional anesthesia [9]. By blocking neural transmission, thus preventing noxious afferent

input from reaching the central nervous system, and by blocking descending efferent activation of the sympathetic nervous system, regional analgesia can reduce excessive stress response from surgery and lessen its resulting immunosuppression [5,6]. Experimental evidence also suggests that preemptive analgesia can effectively attenuate peripheral and central sensitization to pain, thereby decreasing the potential for development of chronic pain syndromes [6].

Local anesthetics also block voltage gated sodium channels, interfering with membrane depolarization and conduction of the pain impulse [5]. Regional anesthesia is often referred to as the "Cadillac of pain control," and peripheral nerve blocks (PNBs) provide an excellent alternative to conventional multimodal therapy. Local anesthetics produce transient loss of sensory, motor and autonomic function when delivered proximal to neural tissue. They can be used for surgical anesthesia and pain control, in many forms, including topically for surface anesthesia, injected for infiltration or field blocks, peripheral nerve blocks, epidural or spinal anesthesia, or intravenous regional anesthesia (Bier's block). Local anesthetics can be used alone or mixed with opioids and administered neuraxially [9]. They can also occasionally be used systemically in patients with neuropathic pain, by producing sedation, central analgesia and an interruption in the pain cycle [5,9]. Lidocaine, procaine, and chlorprocaine are the most commonly used agents due to markedly improved safety margins [5]. Choice of anesthetic during surgical procedures has been shown to affect cancer outcomes. For example, recent research has revealed that anesthetic technique has an impact on breast cancer recurrence. In a retrospective analysis, patients receiving neuraxial or paravertebral nerve block anesthesia for breast cancer surgery demonstrated a lower cancer recurrence rate, as well as an improved survival rate through 36 months of follow up [10]. A multicenter, prospective, randomized trial is currently underway to validate these findings and should help illuminate the way forward to optimize patient outcomes such as these [11]. In vitro analysis of breast cancer cells taken from patients receiving either general anesthesia (inhalational agent maintenance) or paravertebral catheter (continuous peripheral nerve block) and general anesthesia (propofol maintenance), revealed significant inhibition of cancer cell proliferation in the regional/GA group [12].

These positive effects have yet to be as clearly established for other cancer types. Two retrospective analyses of patients undergoing prostate cancer surgery with or without epidural anesthesia revealed a decreased risk of biochemical cancer recurrence [13], and enhanced survival up to 18 months [14] in the epidural study groups. In a more recent retrospective secondary analysis, however, there was no observed difference in disease free survival between the epidural and control groups after radical prostatectomy (4.5 year median follow up) [15]. Ultimately, this illustrates the need for further research to evaluate whether epidural or other regional anesthesia techniques impart a sustained survival benefit for various cancers. The potential to customize an anesthetic plan to the individual patient and their particular malignancy remains an area in which the perioperative team may affect improved patient outcomes.

PAIN MANAGEMENT FOR RADIATION ONCOLOGY

Surgical procedures are not the only cancer related treatments necessitating the use of anesthesia radiation treatments often have specific requirements that pose unique challenges for the anesthesiologist [16,17]. For example, children undergoing external beam radiation often require daily intubation to facilitate immobilization during the radiation treatment. Depending on the site being irradiated, they may be placed prone a position that results in physiological changes, which can lead to adverse outcomes. These include injury to the central and peripheral nervous systems, soft tissue injuries such as decubitus ulcers, as well as ophthalmic and embolic complications [18]. These risks are

compounded in the setting of daily radiation treatments administered over the course of several weeks.

For patients undergoing brachytherapy (internal radiation), there may be a significant amount of procedure related pain related to place ment of the brachytherapy instruments. These patients may be required to remain immobile for several days at a time, as it is essential that the equipment remain stationary within the patient. However, multiple transfers between various hospital departments are frequently necessary during the planning process. Regional anesthesia techniques can pro vide a reasonable solution to this paradoxical problem, offering suffi cient analgesia and immobilization while allowing for increased ease and safety of transfer without disruption of the brachytherapy system. Examples include spinal or epidural anesthesia, booth single shot and continuous catheter techniques. By improving pain control, regional anesthesia has been shown to decrease the incidence of early cessation of brachytherapy due to patient discomfort, as can occur with manage ment via non steroidal anti inflammatory drugs and opioids [19].

CHRONIC PAIN MANAGEMENT

Chronic pain management is of paramount importance in this popu lation of patients undergo definitive surgery, radiation and chemother apy with treatment associated discomfort and break through pain, as well as those with advanced disease and tumor related symptoms associated with baseline or chronic pain. Interventional approaches used for the treatment of cancer pain include neurolytic techniques; the most common being sympatholytic blocks of the celiac plexus, lumbar sympathetic chain, hypogastric plexus, and ganglion impar. Lumbar sympathetic blocks, while usually used for management of Complex Regional Pain Syndrome (CRPS) or painful diabetic neuro pathy of the lower extremities, can also be used for chronic intractable pelvic pain [20 23]. Neurolytic celiac plexus block targets pain from intra abdominal malignancies such as pancreatic cancer. Hypogastric plexus, or ganglion impar neurolytic blocks are often used for malignant tumors of the pelvis, while a neurolytic saddle block can help with refractory pelvic pain. Likewise, neurolytic intercostal blocks can pro vide pain relief in patients with rib metastases [5,6].

Newer anesthetic techniques can allow for improved pain control in these patients. One illustrative example is for patients with advanced pancreatic cancer undergoing directed pain management via neurolytic celiac plexus blocks (NCPB). A study from the Mayo clinic [24] followed 100 patients with unresectable pancreatic cancer, randomly assigned to receive either NCPB or systemic analgesic therapy alone with a sham injection. A larger decrease in pain intensity was seen in the NCPB group, both in the first week after randomization (P 0.005) and over time (P 0.01). Also, fewer NCPB patients reported moderate or severe pain in the first 6 weeks (14% vs. 40% in the opioid only group, P 0.005). However, quality of life and survival were not affected in this study. This data was examined in a recent systematic review of 5 randomized controlled trials with NCPB [25], which showed a decrease in opioid consumption (at 2, 4 and 8 weeks) and associated reduction in constipation (relative risk 0.67, 95% CI 0.49 0.91). This example demonstrates the potential role of more advanced anesthesia techniques for cancer patients, and suggests the need for further study in this area.

MOLECULAR ADVANCES IN PAIN

Our understanding of genetic variations that affect nociception and pain perception and response, as well as response to anesthetics and analgesics, has grown considerably in recent years. These advances provide the potential to customize pain management and anesthesia to improve pain control and patient satisfaction. Emerging evidence also suggests that these individual genetic variations governing response to anesthetics and analgesics may impact outcomes such as cancer

recurrence and mortality. A few of the most well understood examples of genetic polymorphisms implicated in pain and response to anesthetics and analgesics will be discussed below; for a more detailed examination of this topic, we refer readers to several review articles that analyze recent advances in pain genetics in depth [26 30].

Genetic polymorphisms that are linked to altered pain phenotypes are found in a variety of genes, including genes that code for receptors [31 35], transcription factors [36], cytokines [37 39], enzymes [40 42], ion channels [43,44], and neurotrophins [45]. These polymorphisms are most often single nucleotide polymorphisms (SNPs) that may or may not alter the amino acid sequence of the protein encoded by the affected gene. SNPs can cause nonsense mutations giving rise to non functional proteins [43]. Other consequences of some SNPs include altered mRNA and/or protein levels resulting from a variety of mechanisms, including differences in transcriptional or translational efficiency as well as effects on mRNA or protein stability [46,47]. Other important functional con sequences of SNPs are potential changes in the rate of enzyme catalysis [30,40] or ligand binding affinity [48].

Human genetic linkage mapping identified genetic variants found in familial pain disorders. These studies found links between SNPs in *SCN9A*, which encodes the $Na_v1.7$ sodium channel highly expressed in peripheral neurons, and both pathological pain disorders and congenital insensitivities to pain [49]. Examination of families and sporadic cases identified multiple missense mutations in *SCN9A* which altered channel activation inducing a gain of function phenotype. These missense mutations result in primary erythermalgia, characterized by burning pain in the extremities, and paroxysmal extreme pain disorder (PEPD), which causes rectal, ocular, and submandibular pain [50,51]. Conversely, at least three nonsense mutations in *SCN9A*, resulting in channel loss of function, are linked to congenital insensitivity to pain [43]. The significance of this gene for nociception is further underscored by a recent report identifying a linkage between SNP rs6746030 and pain perception. The less common A allele was associated with decreased pain threshold as compared to the more common G allele in healthy subjects as well as in patients experiencing pain [52]. These data identify the $Na_v1.7$ sodium channel as a central mediator of nociception.

Much research has been focused on understanding differences in opioid requirements among individuals. The strongest link between pain and response to opioids and genetic variation is found with the gene that encodes cytochrome p450 2D6, *CCYP2D6*. Variants of this gene deter mine the rate at which opioids and other drugs are converted to active molecules in the body, and multiple SNPs have been identified that affect the metabolism of codeine, tramadol, hydrocodone, oxycodone, and tricyclic antidepressants [53]. More than 60 alleles of *CCYP2D6* are found in humans and can affect the ability of the enzyme to metabolize drugs. Patients with two non functional alleles are poor metabolizers and exhibit decreased drug response and altered drug clearance. One or two functional alleles result in the extensive metabolizer phenotype, whereas the presence of one non functional and one functional allele give rise to an intermediate metabolizer phenotype. Patients categorized as extensive or intermediate metabolizers make up the majority of the population, although they can still exhibit variation in response to drugs based on other factors. People with more than two functional copies of *CCYP2D6* are ultra rapid metabolizers and are at risk for increased pharmacodynamic effects of drugs metabolized by the enzyme [54 56].

Other genes linked to pain and response to anesthetics and analgesics have been identified, including *COMT* (catechol O methyltransferase), *MCR1R* (melocortin 1 receptor), and *OPRM1* (mu 1 opioid receptor), and intensive investigation into the implications of these genetic vari ations is ongoing [26,27,56]. Elucidating genetic polymorphisms associated with pain and anesthetic and analgesic usage could have important implications for the treatment of many diseases, including cancer. Multiple studies have suggested that the use of regional anes thesia in surgical interventions for breast, colon, and prostate cancer

could result in decreased cancer recurrence rates as compared to patients who did not receive regional anesthesia [10,13,14,57]. The authors of these studies suggest that this effect on outcome could be due to a decreased surgical stress response, resulting in lesser immunosuppression, better pain control, and a decrease in opioid requirements for these patients. One intriguing possibility is that patients who possess alleles resulting in altered sensitivity to pain or opioid metabolic capability could receive an even greater benefit from the use of regional anesthesia. This idea requires further investigation to determine its validity. It is clear, however, that a better understanding of the molecular biology and the genetics of pain may translate into better outcomes; improving both patient and clinician satisfaction with regards to the care of cancer patients.

FUTURE CONSIDERATIONS AND IMPLICATIONS

For various reasons, the de facto methodology for most anesthetics done in the United States is a general anesthesia with opioid analgesia strategy. Yet contemporary research has clearly established the immune modulating effects of both volatile anesthetics [58,59] and opioids [60,61]. This is an area within the perioperative care of the cancer patient where a simple modification of the conventional paradigm may bring about significant improvements in patient outcomes.

Antecedence must also be given to the optimization of pain control along the entire continuum of care, beginning preemptively when possible, sustained through the operative or therapeutic course, and continuing throughout the hospitalization and postoperative course; all the while relying heavily on non opioid medications so as to avoid physical dependence. Another priority is developing therapeutics that allow for provision of analgesia without depressing respiration and circulation. Specifically, alternate medications should be based on drugs with reduced opioid content, or even non opioid drugs. Morphine, fentanyl and other opioids, while effective analgesics, are also cardiorespiratory depressants. One such medication, ketamine, continues to emerge as a clinically effective alternative to morphine and its opioid relatives. This NMDA antagonist decreases opioid consumption and minimizes the impact of narcotics on gastrointestinal motility. Particularly attractive features include multiplicity of options for routes of administration (IV, IM, PO, PR, SL, topical/transdermal) and a wide therapeutic range allowing for the one drug to be used for varying degrees of care from subtotal analgesic to complete anesthetic depending on clinical context. S ketamine, a stereoselective isomer of ketamine, may prove to be even more beneficial as it affords the option of monotherapy for multiple indications to include peri procedural sedation and intra operative anesthesia as well as out patient analgesia for acute and/or chronic pain [62 64].

In terms of advancing medical therapy, S ketamine is viewed by the authors as "low hanging fruit"; a potential high yield analgesic alternative which stands out as a significant improvement in patient care once approved through the FDA. With reports of a safer therapeutic index, greater analgesic potency and fewer psychomimetic side effects than racemic ketamine, the S enantiomer is anxiously awaited by clinicians and patients alike. In prospective studies, S ketamine has been shown to be an effective analgesic for acute pain, chronic pain, and as an adjunct for total intravenous anesthesia [62 65]. The benefits of using the specified isomer include a more rapid elimination profile, effective analgesia persisting after termination of infusion, and an improved recovery profile [64,66,67].

CONCLUSION

Cancer pain is horrible indeed, all sub optimally managed pain is agony. Whether it is the time honored dose of 10 mg of morphine or the

state of the art technology of immersive virtual therapy combined with developmental drugs in the FDA pipeline, optimal anesthetic care and successful analgesia reduces pain and suffering while improving clinical outcomes and the patient's quality of life. There are several pharmaceutical products in the developmental pipeline that are awaiting full review and FDA clearance. Transdermal PCA's rely upon iontophoretic principles while intranasal drug delivery devices utilize rapid mucosal uptake to maximize drug delivery. Other recent technological advancements involving nanotechnology and the "pain vaccine" carry the potential to provide prolonged benefit with analgesic durations lasting from hours to days at a time, without the negative sequelae of opioids. Perhaps the most promising potential medications are those non opioid, non mu receptor based therapeutics which prove to be potent analgesics with improved side effect profiles the next major advancement in pain control.

Another cutting edge of advancing practice is the use of genomic mapping technologies to create specific analgesic treatment plans. As highlighted above, the science behind these theories has advanced substantially. It is anticipated that within this decade we will be able to use each individual patient's genotype and couple it with gene mapping technologies to pre operatively develop a comprehensive perioperative anesthetic and analgesic plan, designed specifically to mitigate the negative side effects of surgery. With this technology, chronic pain could also be targeted. Ultimately, this stands to marginalize chronic pain syndromes and other long term pain sequelae, such as PTSD, depression and sleep disturbances, making them a phenomenon of the past. Clinicians could optimize perioperative care by individualizing it, allowing for exemplary medical management, and improved pain control with greater precision for any given cancer patient. More research and development is needed to study and validate these possibilities. Anesthesia and pain research will continue to light the way for clinicians and their patients alike. The interplay of sub optimal pain management and its effects on day to day activities cannot be under estimated. Society pays the bill of pain in the currency of work hours lost, healthcare dollars spent and lives disrupted. Many times these lives are completely uprooted, and entire families are destroyed. The problems these patients and their loved ones face on a daily basis are a reminder of this moral imperative the need for us to continue our efforts to optimize and improve pain management and to provide our patients an escape from the dire consequences of poor pain control.

ACKNOWLEDGMENTS

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